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Genetic Study of Scaphocephaly

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From a series of 1,408 patients with craniosynostosis hospitalized between 1976 and 1994, 561 probands with non-syndromal isolated sagittal synostosis were analyzed. The prevalence of sagittal synostosis was estimated in the order of 1 in 5,000 children. Family information was obtained from 373 probands distributed among 366 families. The male:female ratio was 3.5:1. There was no maternal or paternal age effect. In 22 of the 366 pedigrees, a high degree of familial aggregation was observed, giving a 6% figure of familial cases. Segregation analysis of 253 families indicates that sagittal synostosis is transmitted as a dominant disorder with 38% penetrance and 72% of sporadic cases. The frequency of twinning was 4.8% with only 1 concordance for sagittal synostosis in a monozygotic twin pair. The possibility of a mechanical pathogenesis in sporadic cases is discussed. © 1996 Wiley-Liss, Inc.

KEY WORDS: craniosynostosis, sagittal synostosis, scaphocephaly, genetics, autosomal dominant, segregation analysis

INTRODUCTION

Scaphocephaly is a birth defect defined as a premature craniosynostosis involving the sagittal suture, and is the most frequent of the craniosynostoses seen in western countries [Anderson and Geiger, 1965; Cohen, 1986; Hunter and Rudd, 1976; Shillito and Matson, 1968]. Of 1,408 patients with craniosynostosis admitted to the Department of Pediatric Neurosurgery at the Hôpital Necker Enfants-Malades in Paris between 1976 and 1994, 561 (39.8%) were scaphocephalic. The prevalence of craniosynostosis in France is estimated at 1 in 2,100 children [Lajeunie et al., 1995], giving a prevalence of scaphocephaly of 1 in 5,250 children. This figure is presumably an underestimation as an unknown proportion of cases are not recognized or not referred for consultation.

Few studies have dealt with the genetics of scaphocephaly [Hunter and Rudd, 1976]; usually most cases are described as sporadic. A rate of 2% of familial instances was published by Anderson and Geiger [1965] and by Hunter and Rudd [1976]. In their excellent study, Hunter and Rudd concluded: "Familial data and the skull measurements of a sample of parents of affected children were compatible with multifactorial inheritance; however there is need for prospective family studies and parental measurements on ethnically uniform groups." The present study examines the pattern of transmission of primary, non-syndromal isolated scaphocephaly by analyzing the family histories of 373 probands.

MATERIAL AND METHODS

Between 1976 and 1994, 1,408 patients were admitted to the Hôpital Necker Enfants-Malades with craniosynostosis; 561 of them had an isolated, non-syndromal sagittal synostosis. This diagnosis was made by direct examination by the same craniofacial team (DR and DM). Details of the specific suture involved were taken from radiological and operative records. Patients with additional suture involvement were excluded. Careful attention was paid to exclude individuals with additional abnormalities which are present in well known craniosynostosis syndromes; 65% of the total patient group with scaphocephaly underwent surgery.

Three hundred seventy-three probands were distributed among 366 pedigrees. Information was obtained through contact with the families, in person or by telephone. Information regarding birth weight, birth order, maternal and paternal age at the time of birth, maternal and paternal ethnic origin and associated malformations was collected for first and second degree relatives and for first cousins.

Segregation analysis was performed on 253 nuclear families, i.e., on families with more than one sib. We used the scoring procedure developed by Fisher and

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adapted for segregation analysis by Morton [1958]. The model is characterized by a proportion x of sporadic cases and a proportion $1 - x$ of genetic inherited cases with a segregation frequency p. The segregation frequency is the probability that a child be affected in multiplex and simplex families of the same origin, where sagittal craniosynostosis segregates. This frequency is supposed to be the same in all families and is characteristic of the transmission mode of the disease. Details of the calculations have been described elsewhere [Lajeunie et al., 1995]. The probability of ascertainment π is a parameter of segregation analysis. It is estimated from the distribution from probands among affected cases in sibships with at least two affected cases by the maximum likelihood method [Morton, 1959].

Familial data on congenital malformations are usually ascertained through children. Our method of segregation analysis used only nuclear families with an affected child. The study of offspring of affected persons is expected to provide additional information and in addition in the present study a difference in frequency with sex was observed. We used the POINTER program developed by Lalouel et al. [1983] on our data. This program can show a major gene effect with a residual polygenic component and environmental effects. The extended pedigrees are separated into nuclear families and in the present study sex specific liabilities were considered.

RESULTS

Neonatal Data

The average birth weight was 3,247 ± 648 g (n = 336), which is consistent with reported norms. Average maternal age was 29.6 ± 4.8 years (n = 357, range 16–43) and the average paternal age was 32 ± 6 years (n = 352, range 19–57) at the child's birth. The age distribution shows that 151/357 (39.5%) of the mothers and 86/352 (24.4%) of the fathers were respectively over 30 and 35 years of age at the birth of their child. The control data chosen were all live births registered by INSEE (Institut National des Statistiques et des Etudes Economiques) for the same period. The distribution of maternal or paternal age in the present series was not different from the normal population.

There is a strong male preponderance in our series. The total group (n = 561) consisted of 436 (77.7%) males and 125 (22.3%) females, giving a male:female ratio of 3.5:1.

Eighteen of the 373 (4.8%) probands were members of a twin pair. There were 4 females (22.2%) and 14 males (77.8%), a distribution similar to the whole series. Nine sets of twins were dizygotic (no concordance) and four were monozygotic (1 concordant for scaphocephaly). In five sets the zygosity was unknown. The affected child was the first born in 4 sets of twins, the second in 12 sets, and the birth order was unknown in 2 cases.

Five children (0.9%) had associated malformations. Three had a congenital heart disease and two had a urinary tract malformation.

Segregation Analysis

Three hundred and seventy-nine children (373 probands) with sagittal synostosis occurred in 366 families (Table I). There were only one sib, two sibs and more than two sibs in respectively 113, 136, and 117 nuclear families. There was a proven family history of scaphocephaly in 22 families (6%), corresponding to 35 affected children in nuclear families of probands. Pedigrees of familial cases are presented in Figure 1. Eleven families demonstrated horizontal recurrence with normal parents and more than one affected child. In four families, the father of the proband was affected. Seven families had obligate but non-manifesting carrier parents.

In four families (not included in the present series) an affected member presented with sagittal synostosis while another one had a different fused suture. In the three sibs of the first family, the first (male) had a scaphocephaly, the second (female) was normal, and the third (male) had trigonocephaly. In the second family, the mother was affected by unicoronal synostosis; she had a normal daughter and a son with sagittal synostosis. In the third family, the two sibs were affected: a male with trigonocephaly and a female with scaphocephaly. In the fourth family, the father had a daughter with scaphocephaly and a first cousin with plagiocephaly.

Using the distribution of probands among affected cases in 13 sibships, we could estimate the probability of ascertainment as 0.78. The estimate of the segregation ratio p was 0.19 (SD 0.07), leading to a 38% estimate for penetrance, under a dominant mode of transmission. Among families without affected parents, the estimated proportion of sporadic cases was 0.75 (SD 0.10). Thus, this proportion was 0.72 in the whole sample. So, primary sagittal craniosynostosis has an autosomal dominant mode of transmission with low penetrance and 72% of sporadic cases.

TABLE I. Distribution of 366 Sibships According to Disease Status of Parents

Disease status of parents	Number of sibships	Number of sibs			
		Affected		Unaffected	
		Males	Females	Males	Females
Both parents unaffected	344 sporadic cases	274	70	194	196
	11 familial cases	17	5	6	2
Carrier or affected parent	11	9	4	8	6
Total	366	300	79	208	204

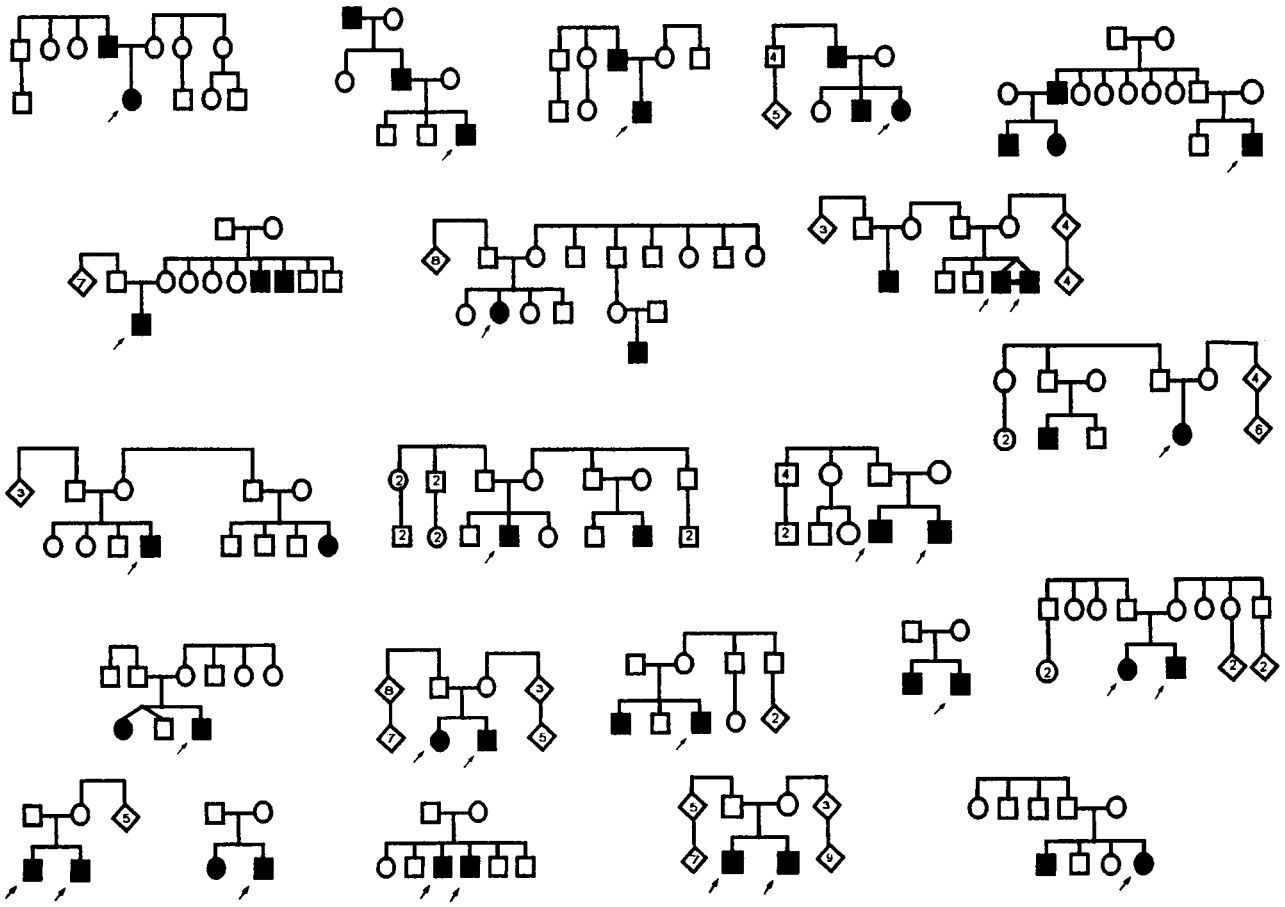

Fig. 1. Pedigrees of the 22 families with scaphocephaly.

The POINTER program was not suitable for our data. Under the polygenic inheritance model, no converged solution could be obtained. Using the monogenic model, the likelihood of different hypotheses were similar: different models of inheritance are equally plausible.

DISCUSSION

Patients with sagittal synostosis represent 39.8% (561/1,408) of all forms of craniosynostoses admitted to our Department of Pediatric Neurosurgery. In the literature, the proportion of sagittal synostosis varies greatly with three large North American series [Anderson and Geiger, 1965; Hunter and Rudd, 1976; Shillito and Matson, 1968] giving rates of approximately 56%, while in two Mediterranean series the incidence was found to be of the order of 19% [Acquaviva et al., 1966; Colak et al., 1992]. This geographic difference may be explained by the increased incidence of oxycephaly in Mediterranean countries—a craniosynostosis which is considered very rare in the other parts of the world [Gault et al., 1989; Renier and Marchac, 1995]. As compared with the American series, the present one has a lower incidence of sagittal synostosis. This probably represents local referral patterns with a higher percentage of complex craniosynostoses being referred to our department, while scaphocephalics are often treated in their regional hospital. This is confirmed by the probability of ascertainment which was estimated in the present series at 0.78.

In the present series of 561 sagittal synostoses, there was a male:female ratio of 3.5:1. This ratio is similar to most published series [Hunter and Rudd, 1976; Shillito and Matson, 1968; David et al., 1982]. Male predominance is the rule in sagittal synostosis, whereas in coronal synostoses females are twofold more affected than males [Lajeunie et al., 1995].

Paternal or maternal age had no significant effect in scaphocephaly when compared with the distribution of parental age in our control group, suggesting that fresh autosomal dominant mutations are an unlikely explanation for sporadic cases, which represent most scaphocephalies.

The present genetic analysis concerns 373 probands representing 66.5% (373/561) of sagittal craniosynostosis in the present series. These probands were distributed among 366 pedigrees and we found 22 families (6%) with a high degree of familial aggregation. If all the families in which no genetic study could be established consisted of non-familial cases, the proportion would be 4% (22/554). In the previous published series the percentage of familial cases was 2% [Anderson and Geiger, 1965; Hunter and Rudd, 1976]. Hunter and

Rudd [1976] reported more than one affected individual in three families. In Shillito and Matson's series [1968], four pairs of sibs had sagittal synostosis. David et al. [1982] described one male infant whose father and older brother had scaphocephaly. These lower recurrence rates in families as compared with our own may be explained by the fact that parents of an affected sib are often normal and incomplete studies of various relatives may result in a spuriously high rate of sporadic cases. Our series emphasizes the need for a careful genetic history.

Vertical and male to male transmission of the trait establishes the autosomal dominant pattern. Most of the parents of affected sibs were not affected themselves but obviously carried and transmitted the deleterious gene. This can be considered as evidence of reduced penetrance. We report here the first segregation analysis for sagittal premature synostosis performed on a sample of 253 pedigrees. In this study, the defect was transmitted as a dominant disorder with 38% penetrance and 72% sporadic cases. A previous study [Lajeunie et al., 1995] allowed us to conclude that nonsyndromal coronal craniosynostosis (14.4% familial cases) is also transmitted as an autosomal dominant trait with 60% penetrance and 61% sporadic cases. The finding of normal mean paternal age and low penetrance suggests that scaphocephaly is more common in parents of affected children than observed in the present series. In fact, scaphocephaly is difficult to recognize either clinically or radiologically in adults, except in the most severe cases.

The cause of the scaphocephaly in sporadic cases remains unknown. An interesting hypothesis of in utero head constraint has been suggested [Graham et al., 1979; Higginbottom et al., 1980]. The frequency of twinning in the present series seems to reinforce this hypothesis. We found 18 affected twins including one monozygotic pair with concordant scaphocephaly among our 373 cases. If the frequency of twin pregnancies in the general population is taken as 1/80, then we would expect 1 person in 40 (2.5%) to be a twin. In our series, the rate of twinning was 4.8%, which is significantly higher ($P < 0.01$). In Hunter and Rudd's series [1976], 7 of the 214 probands (3.3%) were members of a twin pair, but this failed to reach significance. The relatively high incidence of twinning in the present series may be further evidence that a crowded uterus may result in fetal head constraint and lead to premature craniosynostosis. Also of interest in our series is the fact that the affected child of twin sets was significantly more frequently the second born ($P = 0.05$). In the light of these observations, it is apparent that besides genetically caused sagittal synostoses, some cases may be due to mechanical factors.

Scaphocephaly, with few familial cases, appears to be heterogeneous, including different modes of inheritance and possibly non-genetic causes. Investigation with polymorphic markers may prove helpful in elucidating the mode of inheritance and the genes implicated. Recently, mutations in the fibroblast growth factors receptors (FGFR)1 and 2 have been shown to cause Crouzon [Reardon et al., 1994], Pfeiffer [Lajeunie et al., 1995; Muenke et al., 1994; Rutland et al., 1995] and Apert [Wilkie et al., 1995] syndromes where craniosynostosis is associated with other abnormalities. In view of these findings, a linkage approach should be used in non-syndromal craniosynostoses to test candidate genes with markers around the four FGFR loci.

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